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(71) Applicant *(for all designated States except US)*: OTSUKA PHARMACEUTICAL COMPANY, LIMITED [JP/JP]; 9, Kandatsukasa-cho 2-chome, Chiyoda-ku, Tokyo 101 (JP).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: KOMATSU, Makoto [JP/JP]; 91-5, Sasagino-Aza-Hachiyamakaitaku, Matsushige-cho, Itano-gun, Tokushima 771-02 (JP). UCHIDA, Minoru [JP/JP]; 11, Aza-Motomura, Obayashi-cho, Komatsushima-shi, Tokushima 773 (JP). NISHI, Takao [JP/JP]; 2-28, Tarobachizu-Aza-Sotobiraki, Kitajima-cho, Itano-gun, Tokushima 771-02 (JP).

(74) Agents: AOYAMA, Tamotsu et al.; Aoyama & Partners, IMP Building, 3-7, Shiromi 1-chome, Chuo-ku, Osaka-shi, Osaka 540 (JP).

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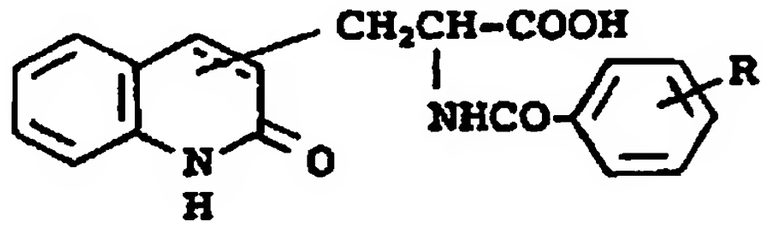
(54) Title: BISMUTH SALT OF CARBOSTYRIL DERIVATIVES FOR THE TREATMENT OF PEPTIC ULCERS

(57) Abstract

Bismuth salt of carbostyril derivatives of formula (I) wherein R is a halogen atom, the propionic acid substituent is substituted at 3- or 4-position on the carbostyril nucleus, and the bond between 3- and 4-positions is single or double bond, which is useful for the prevention and treatment of peptic ulcer and peptic inflammatory diseases.



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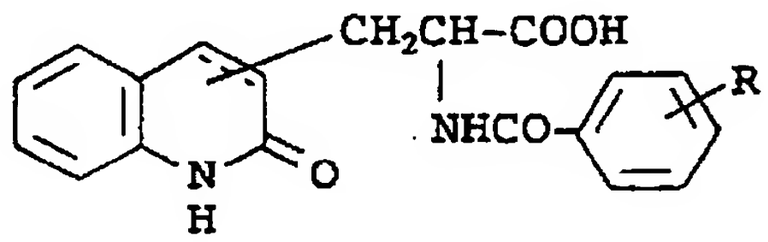
DESCRIPTION

BISMUTH SALT OF CARBOSTYRIL DERIVATIVES FOR THE TREATMENT OF PEPTIC ULCERS

Technical Field

This invention relates to a novel bismuth salt of carbostyril derivatives useful as a medicament. More particularly, it relates to a bismuth salt of carbostyril derivatives of the formula:



(I)

wherein R is a halogen atom, and the propionic acid substituent is substituted at 3- or 4-position on the carbostyril nucleus, and the bond between 3- and 4-positions is single or double bond, preferably a bismuth salt of 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid.

Background Art

The carbostyril derivatives of the formula (I) and processes for the preparation thereof are disclosed in Japanese Patent Second Publication (Kokoku) No. 35623/1988. It is disclosed that the carbostyril derivatives are useful as an anti-ulcer drug (Japanese Patent Second Publication (Kokoku) No. 61923/1990). It is also known that these carbostyril derivatives are useful as an agent for the treatment of gastritis (Japanese Patent First Publication (Kokai) No. 74329/1991) and further as an anti-diabetic (WO 92/21342 and Japanese Patent First Publication (Kokai) No. 148143/1993), as an agent for increasing somatostatin or for inhibiting decrease

of somatostatin (WO 93/23043), and as an agent for protecting intestinal mucous membrane disorder or for treating ulcerative colitis (Japanese Patent First Publication (Kokai) No. 211662/1994).

It has recently been found that a Gram-negative bacteria, *Helicobacter pylori* participates significantly in induction of various diseases such as chronic gastritis, stomach ulcer, duodenal ulcer, etc. [cf. Masaaki TOMOI, Pharmacia, Vol. 29, No. 8 (1993), pp. 873-876]. For example, in patients suffering from an active chronic gastritis, *Helicobacter pylori* has been detected in such a high ratio as 88 % in average, and it has been found that the number of cells of *Helicobacter pylori* is correlative with the degree of the symptom of chronic gastritis accompanied with increase of neutrophil and permeation of lymphocytes (which are index for the activity of the gastritis). It is also disclosed in the above literature that in case of patients suffering from duodenal ulcer, the infectious ratio of *Helicobacter pylori* is in such a high ratio as 85 % in average, and hence, this bacteria participates significantly in said disease. It is also known that when these patients stop to take a drug, the diseases will again appear. When an antibacterial agent is administered to the patients, the recurrence of the diseases is significantly decreased. Accordingly, it will be considered that *Helicobacter pylori* participates in the recurrence of gastritis, duodenal ulcer, etc.

It is known that the infection of *Helicobacter pylori* can be remedied by administering the patients a bismuth salt

(e.g. colloidal bismuth subcitrate or bismuth subsalicylate) or an antibacterial agent (e.g. amoxicillin, tetracycline, etc.) alone, or a combination of a bismuth salt, an antibacterial agent and an antiprozoal (e.g. metronidazole). (Journal of Antimicrobial Chemotherapy (1986) Vol. 17, pp. 309-314). It is also known that bismuth or some bismuth salts are useful for the treatment of gastrointestinal disorders (EP-A_2-0206626, EP-E_2-026627, Japanese Patent First Publication (Kokai) No. 48624/1987).

Summary of the Invention

The present inventors have studied to develop a new drug having a specifically high inhibitory activity against *Helicobacter pylori* with less side effects and have found that the novel bismuth salt of carbostyril derivatives of the formula (I), particularly 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid bismuth salt, show superior antibacterial activity against *Helicobacter pylori* and are useful as a drug for the treatment of peptic ulcers (e.g. gastric ulcer, duodenal ulcer, etc.) and for the treatment of peptic inflammation diseases (e.g. gastritis) and further that the compounds of this invention show excellent preventive or therapeutic effects on chronic ulcer models such as experimental ulcer induced by acetic acid or thermal ulcer, or on various other experimental ulcer models and also therapeutic effects on gastric inflammation with less toxicity and less side effects and hence are useful as an agent for the prevention or treatment of chronic ulcers. Thus, an object of the invention is to provide a novel bismuth salt of

carbostyril derivatives (I) useful as a drug. Another object of the invention is to provide an antibacterial agent for the treatment of *Helicobacter pylori* infectious diseases, or an anti-peptic ulcer agent, or an anti-peptic inflammatory agent. A further object of the invention is to provide a drug for the prevention and treatment of various inflammatroy diseases and various chronic ulcers.

Brief Description of Drawings

Fig. 1 shows a chart of IR spectrum of the compound of this invention prepared in Example 1.

Fig. 2 shows a chart of IR spectrum of the compound of this invention prepared in Example 2.

Disclosure of the Invention

The bismuth salt of the carbostyril derivatives (I) of this invention has an inhibitory activity against *H. pylori* which would participate in occurrence or recurrence of gastric mucouse membrance disorders, for example, inhibitory activities against the promotion of IL-8 production in IL-8-producing cells (e.g. peripheral blood monocyte, tissue macrophase, large granular lymphocyte, T-lymphocyte, neutrophile, fibroblast, vascular endogenic cells, cutaneous keratinocyte, hepatic cells, astrocyte, epithelial cells, gastric carcinoma cells, etc.), inhibition of neutrophile activation, or inhibition of adhesive factor-increasing activity. Thus, the compounds of this invention will be useful for the prevention of occurrence or recurrence of gastric mucous membrane disorders which are induced by *H. pyroli*. Besides, *H. pyroli* has not only the action of inducing the activation of neutrophile but also the

action of promoting the expression of ICAM-1 (ligand of CD11b) in vascular endogenic cells and gastric mucous membrance cells, and hence, the compounds of this invention are also effective for inhibiting the promotion of expression of ICAM-1 by *H. pyroli*.

The compounds of this invention have also an antiulcer activity, an activity of increasing endogenic prostaglandin E_2, an activity for removing or inhibiting active oxygen, an IL-8 production inhibitory activity, an activity for inhibiting activation of granulocytes, an activity for inhibiting expression of adhesive factor of granulocytes, and are useful as an antiulcer agent, an agent for exhibiting activity owing to prostaglandin E_2 (e.g. prevention and treatment of ulcers), an antioxidant, an agent for prevention, protection and treatment of acute or chronic inflammatory diseases. The compounds are also useful for enhancing bio-compatibility of artificial organs and artificial blood vessel. The compounds are further effective for the prevention of recurrence of peptic ulcer and peptic inflammation.

The inflammatory diseases include inflammatory skin diseases such as inflammatory keratosis (e.g. psoriasis, etc.), atopic dermatitis, contact dermatitis, and the like; autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE), Behçet's disease, which are chronic inflammatory diseases; inflammatory hepatic diseases such as hepatitis B, hepatitis C, alcoholic hepatitis, chemical allergic hepatitis; inflammatory kidney diseases such as nephritis, glomerulonephritis; inflammatory respiratory

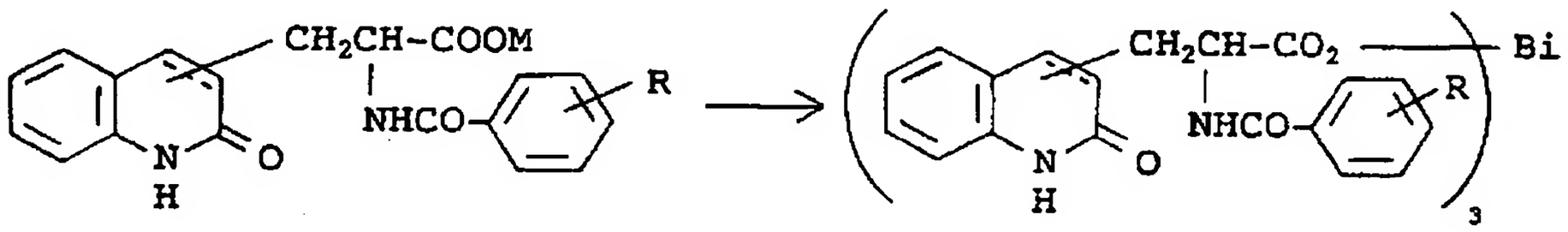
diseases such as bronchitis; aphtha; laryngitis; vocal fold inflammation; voice disorders; inflammatory diseases occurred during using artificial organs or artificial blood vessel; mucous membrane disorders of digestive tract which is induced by non-steroidal antiinflammatories or intestinal mucous membrane disorders; and the like, but are not limited thereto.

The intestinal mucous membrane disorders include simple primary small intestinal ulcer, nonspecific colonic ulcer, ulcerative colitis induced by nonspecific inflammation, Crohn's disease, the cause of which are not yet known, and further includes various disorders induced by infection with microorganisms, disturbances of circulation, collagen disease, irradiation of isotope, or chemicals.

Moreover, the compounds of this invention have inhibitory activity for decrease of secretion of somatostatin, anti-diabetic activity, and urease-inhibitory activity, and hence are also useful as a somatostatin decrease inhibitor, anti-diabetic and urease inhibitor. Owing to the urease-inhibitory activity, the compounds are useful for the prevention and treatment of gastric mucouse membrane disorder caused by production of ammonia induced by *H. pyroli* and further useful for the improvement and treatment of hyper ammonemia or symptoms accompanied with hyper ammonemia by their inhibitory activity against production of ammonia within the intestinal tract, more specifically for the prevention and treatment of hepatic encephalopathy, psychoneurotic disorders, abnormal electroencephalogram, tremor of hand and fingers which appear in hepatic diseases such as hepatitis, cirrhosis.

The compounds of this invention can be prepared by various processes, for example, by the processes as shown in the following reaction schemes.

[Reaction Scheme-1]

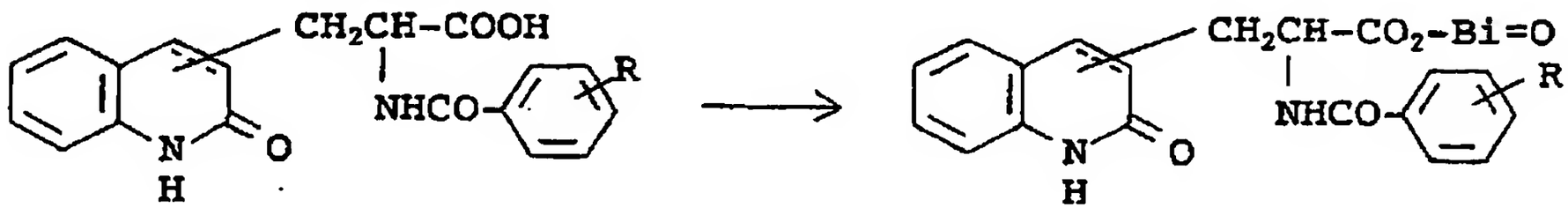


(2a) (1a)

wherein M is an alkali metal such as sodium, potassium, and R, the substituting position of the propionic acid substituent and the bond between 3- and 4-positions are the same as defined above.

That is, the compound (2a) is reacted with bismuth nitrate in an appropriate solvent to give the desired compound (1a). The solvent used therein includes, for example, water, alcohols (e.g. glycerin), preferably a mixture of water and an alcohol. The compound (2a) is used in an amount of at least 3 moles, preferably 3 to 5 moles, to 1 mole of the bismuth nitrate. The reaction is usually carried out at a temperature of about 0°C to 100°C, preferably at about 0°C to 70°C, for about 0.5 to 5 hours.

[Reaction Scheme-2]



(2b) (1b)

wherein R, the substituting position of the propionic acid substituent and the bond between 3- and 4-positions are the

same as defined above.

That is, the compound (2b) is reacted with bismuth hydroxide in an appropriate solvent to give the desired compound (1b). The solvent used therein includes, for example, water. The bismuth hydroxide is used in an amount of at least 1 mole, preferably 1 to 2 moles, to 1 mole of the compound (2b). The reaction is usually carried out at a temperature of about 0°C to 150°C, preferably at room temperature to 100°C, for about 0.5 to 5 hours.

The bismuth salt of carbostyril derivatives of this invention is usually in the form of conventional pharmaceutical preparations, for example, preparations suitable for oral administration such as tablets, pills, powders, granules, capsules, solutions, suspensions, emulsions, and preparations for parenteral administration such as suppositories and injections (e.g. solutions, suspensions, etc.). These preparations can be prepared by a conventional method with conventional pharmaceutically acceptable carriers or diluents, such as fillers, thickening agents, binders, wetting agents, disintegrators, surfactants, lubricants, and the like.

In order to form in tablets, there are used conventional pharmaceutically acceptable carriers such as vehicles (e.g. lactose, white sugar, sodium chloride, glucose, urea, starches, calcium carbonate, kaolin, crystalline cellulose, silicic acid, etc.), binders (e.g. water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethyl cellulose, shellac, methyl cellulose, potassium phosphate, polyvinylpyrrolidone, etc.),

disintegrators (e.g. dry starch, sodium arginate, agar powder, laminaran powder, sodium hydrogen carbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium laurylsulfate, stearic monoglyceride, starches, lactose, etc.), disintegration inhibitors (e.g. white sugar, stearin, cacao butter, hydrogenated oils, etc.), absorption promoters (e.g. quaternary ammonium base, sodium laurylsulfate, etc.), wetting agents (e.g. glycerin, starches, etc.), adsorbents (starches, lactose, kaolin, bentonite, colloidal silicates, etc.), lubricants (e.g. purified talc, stearates, boric acid powder, polyethylene glycol, etc.), and the like. Moreover, the tablets may also be in the form of a conventional coated tablet, such as sugar-coated tablets, gelatin-coated tablets, enteric coated tablets, film coating tablets, or double or multiple layer tablets.

In the preparation of pills, the carriers include vehicles (e.g. glucose, lactose, starches, cacao butter, hydrogenated vegetable oils, kaolin, talc, etc.), binders (e.g. gum arabic powder, tragacanth powder, gelatin, ethanol, etc.), disintegrators (e.g. laminaran, agar, etc.), and the like.

In the preparation of suppositories, the carriers include, for example, polyethylene glycol, cacao butter, higher alcohols, higher alcohol esters, gelatin, semi-synthetic glycerides, and the like.

Capsules can be prepared by charging a mixture of the compound of this invention with the above carriers into hard gelatin capsules or soft capsules in a usual manner.

In the preparation of injections, the solutions,

emulsions or suspensions are sterilized and are preferably made isotonic with the blood. In the preparation of these solutions, emulsions and suspensions, there are used conventional diluents, such as water, ethyl alcohol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol, polyoxyethylene sorbitan fatty acid esters, and the like. In this case, the pharmaceutical preparations may also be incorporated with sodium chloride, glucose, or glycerin in an amount sufficient to make them isotonic, and may also be incorporated with conventional solubilizers, buffers, anesthetizing agents. Besides, the pharmaceutical preparations may optionally be incorporated with coloring agents, preservatives, perfumes, flavors, sweeting agents, and other medicaments, if required.

The amount of the active component, bismuth salt of carbostyril derivatives, of this invention to be incorporated into the preparations is not specified but may be selected from a broad range, but it is usually in the range of from 1 to 70 % by weight, preferably in the range of 5 to 50 % by weight.

The agent of this invention may be administered in any method, and suitable method for administration may be determined in accordance with various forms of preparation, ages, sexes and other conditions of the patients, the degree of severity of diseases, and the like. For instance, tablets, pills, solutions, suspensions, emulsions, granules and capsules are administered orally. The injections are intraveneously administered alone or together with a conventinal auxiliary liquid (e.g. glucose, amino acid solutions), and further are optionally administered alone in intramuscular, intracutaneous,

subcutaneous, or intraperitoneal route, if required. suppositories are administered in intrarectal route.

The dosage of the agent of this invention may be selected in accordance with the usage, ages, sexes and other conditions of the patients, the degree of severity of the diseases, and the like, but is usually in the range of about 0.6 to 50 mg of the active bismuth salt of this invention per 1 kg of body weight of the patient per day. The active compound is preferably contained in the pharmaceutical preparations in an amount of 10 to 1000 mg per the dosage unit.

Examples

The active compounds and agents of this invention are illustrated by the following Examples, Preparations and Pharmacological experiments.

Example 1

2-(4-Chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid (3.7 g) is suspended in water (50 ml) and glycerin (38 ml), and thereto is added sodium hydroxide (400 mg). The mixture is stirred to dissolve to give sodium 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionate. To the mixture is added dropwise a solution of bismuth nitrate pentahydrate (1.6 g) in glycerin (8 ml) and water (10 ml). After the addition, the mixture is stirred at room temperature for one hour. After adding water to the reaction mixture, the precipitates are separated by filtration, washed with water, and then dried to give bismuth 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionate (i.e. the compound of the formula (1a) wherein R is 4-Cl, the bond between the 3- and 4-positions is double bond, and the propionic acid

substituent is substituted at 4-position) (4.1 g) as white powders.

M.p.: 248 - 257°C (decomp.)

Elementary analysis for $C_{57}H_{42}N_6O_{12}Cl_3Bi.2H_2O$:

Calcd.: C,50.55; H,3.42; N,6.21; Bi_2O_3,17.20

Found: C,49.06; H,3.31; N,5.58; Bi_2O_3,16.27.

IR spectrum: as shown in the attached Fig. 1.

Example 2

Bismuth nitrate pentahydrate (4.9 g) is dissolved in acetic acid (20 ml), and the solution is diluted with water (200 ml). The mixture is made alkaline by adding dropwise 25 % aqueous ammonia with stirring. The resulting suspension is centrifuged, and the supernatant is removed off by decantation. To the residue is added water, and the mixture is stirred and again centrifuged. This procedure is repeated three times to give precipitates of bismuth hydroxide. The precipitates of bismuth hydroxide thus obtained are suspended in water (100 ml) and thereto is added 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid (3.6 g). The mixture is stirred for 20 minutes at room temperature and further for one hour at 60°C. After cooling the reaction mixture, the precipitates are separated by filtration, washed with water, and then dried to give bismuth 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionate (i.e. the compound of the formula (1b) wherein R is 4-Cl, the bond between the 3- and 4-positions is double bond, and the propionic acid substituent is substituted at 4-position) (5.7 g) as white powders.

M.p.: 264 - 269°C (decomp.)

Elementary analysis for $C_{19}H_{14}N_2O_5ClBi.2/3H_2O$:

Calcd.: C,37.61; H,2.55; N,4.62; Bi_2O_3,38.40

Found: C,35.71; H,2.69; N,4.11; Bi_2O_3,34.20.

IR spectrum: as shown in the attached Fig. 2.

Preparation 1

Film coated tablets are prepared from the following components.

Components	Amount
2-(4-Chlorobenzoylamino)-3-(2-quinolon-4-yl)-propionic acid bismuth salt	150 g
Abicel (tradename of microcrystalline cellulose, manufactured by Asahi Chemical Industry Co., Ltd., Japan)	40 g
Corn starch	30 g
Magnesium stearate	2 g
Hydroxypropyl methylcellulose	10 g
Polyethylene glycol-6000	3 g
Castor oil	40 g
Ethanol	40 g

The active component of this invention, Avicel, corn starch and magnesium stearate are mixed and kneaded and the mixture is tabletted using a conventional pounder (R 10 mm) for sugar coating. The tablets thus obtained are coated with a film coating agent consisting of hydroxypropyl methylcellulose, polyethylene glycol-6000, castor oil and ethanol to give film coated tablets.

Preparation 2

Tablets are prepared from the following components.

Components	Amount
2-(4-Chlorobenzoylamino)-3-(2-quinolon-4-yl)-propionic acid bismuth salt	150 g
Citric acid	1.0 g
Lactose	33.5 g
Dicalcium phosphate	70.0 g
Pluronic F-68	30.0 g
Sodium laurylsulfate	15.0 g
Polyvinylpyrrolidone	15.0 g
Polyethylene glycol (Carbowax 1500)	4.5 g
Polyethylene glycol (Carbowax 6000)	45.0 g
Corn starch	30.0 g
Dry sodium laurylsulfate	3.0 g
Dry magnesium stearate	3.0 g
Ethanol	q.s.

The active compound of this invention, citric acid, lactose, dicalcium phosphate, Pluronic F-68 and sodium laurylsulfate are mixed. The mixture is screened with No. 60 screen and is granulated in wet with an alcohol solution containing polyvinylpyrrolidone, carbowax 1500 and 6000. If required, an alcohol is added thereto so that the powder mixture is made a paste-like mass. Corn starch is added to the mixture and the mixture is continuously mixed to form uniform particles. The resulting particles are passed through No. 10 screen and entered into a tray and then dried in an oven at 100°C for 12 to 14 hours. The dried particles are screened with No. 16 screen and thereto are added dry sodium laurylsulfate and dry magnesium stearate, and the mixtue is tabletted to form the desired shape.

The core tablets thus prepared are vanished and dusted with talc in order to guard from wetting. Undercoating is applied to the core tablets. In order to administer the tablets orally, the core tablets are vanished several times. In order to give round shape and smooth surface to the tablets, further undercoating and coating with lubricant are applied thereto. The tablets are further coated with a coloring coating material until the desired colored tablets are obtained. After drying, the coated tablets are polished to obtain the desired tablets having uniform gloss.

Preparation 3

An injection preparation is prepared from the following components.

Components	Amount
2-(4-Chlorobenzoylamino)-3-(2-quinolon-4-yl)-propionic acid bismuth salt	5 g
Polyethylene glycol (molecular weight: 4000)	0.3 g
Sodium chloride	0.9 g
Polyoxyethylene sorbitan monooleate	0.4 g
Sodium metabisulfite	0.1 g
Methyl-paraben	0.18 g
Propyl-paraben	0.02 g
Distilled water for injection	10.0 ml

The above parabens, sodium metabisulfite and sodium chloride are dissolved in distilled water of half volume of the above with stirring at 80°C. The solution thus obtained is cooled to 40°C, and the active compound of this invention and further polyethylene glycol and polyoxyethylene sorbitan mono-oleate are dissolved in the above solution. To the solution is

added distilled water for injection to adjust to the desired volume, and the solution is sterilized by filtering with an appropriate filter paper to give an injection preparation.

Pharmacological Test 1

1. Strain used in the experiment:

Standard strains: *Helicobacter pylori* ATCC 43504 and *Helicobacter pylori* ATCC 43526

Clinically isolated strains:

Helicobacter pylori C0001,

Helicobacter pylori C0002, and

Helicobacter pylori C0003

2. Merhod for measuring the antibacterial activity:

The antibacterial activity of the test compound (compound of Example 1) was measured by an agar plate dilution method. That is, the test compound was weighed, dissolved in distilled water and then diluted with distilled water to prepare a series of fold-diluted solutions. The diluted solution was mixed with Brucella agar medium supplemented with 7 % bovine fetal serum (13.5 ml) to prepare a plate medium containing a test compound. Onto the plate medium containing a test compound was inoculated the test strain (1.8×10^8, 1.8×10^6 CFU/ml, 5 µl) by a point inoculator. It was cultured at 37°C for 3 days under faint aerobic condition. The minimum inhibitory concentration (MIC, µg/ml) was determined when any growth of the bacteria was entirely not observed. The MIC was expressed by converting into the content of bismuth of the test compound.

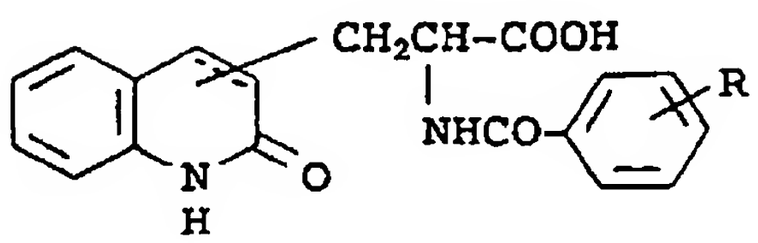
The results are shown in the following Table 1.

Table 1

Strains	MIC of the compound of Example 1 (μg/g)
Helicobacter pylori ATCC 43504	3.98
Helicobacter pylori ATCC 43526	3.98
Helicobacter pylori C0001	3.98
Helicobacter pylori C0002	3.98
Helicobacter pylori C0003	3.98

CLAIMS

1. A bismuth salt of a carbostyril derivative of the formula:



(I)

wherein R is a halogen atom, the propionic acid substituent is substituted at 3- or 4-position on the carbostyril nucleus, and the bond between 3- and 4-positions is single or double bond.

2. A bismuth salt of 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid.

3. A bismuth salt of 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid having an IR spectrum as shown in Fig. 1 which is prepared by reacting sodium 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionate with bismuth nitrate.

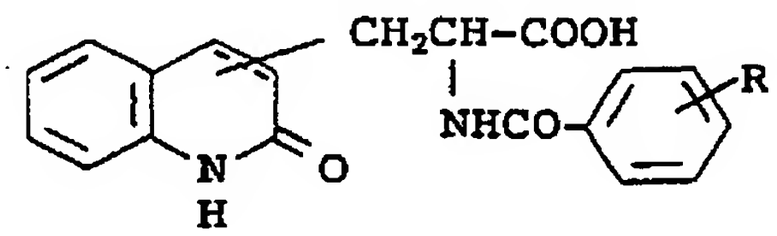
4. A bismuth salt of 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid having an IR spectrum as shown in Fig. 2 which is prepared by reacting 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid with bismuth hydroxide.

5. An antibacterial agent against *Helicobacter pylori*, which comprises as an active ingredient the compound as set forth in claim 1.

6. An agent for the prevention and treatment of peptic ulcer, which comprises as an active ingredient the compound as set forth in claim 1.

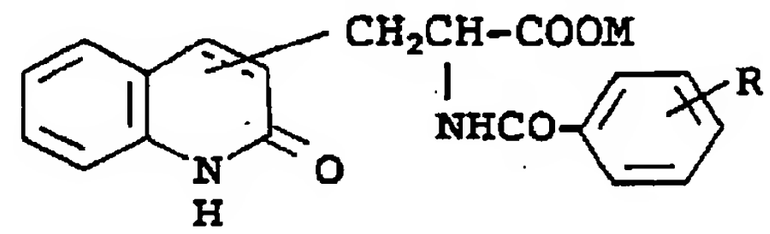
7. An agent for the prevention and treatment of peptic inflammatory diseases, which comprises as an active ingredient the compound as set forth in claim 1.

8. A process for preparing a bismuth salt of a carbostyril derivative of the formula:



(I)

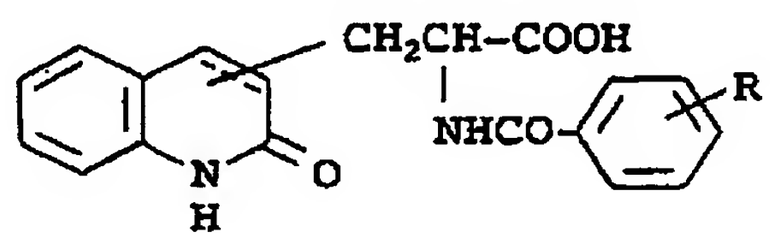
wherein R is a halogen atom, the propionic acid substituent is substituted at 3- or 4-position on the carbostyril nucleus, and the bond between 3- and 4-positions is single or double bond, which comprises reacting a carbostyril compound of the formula:



(2a)

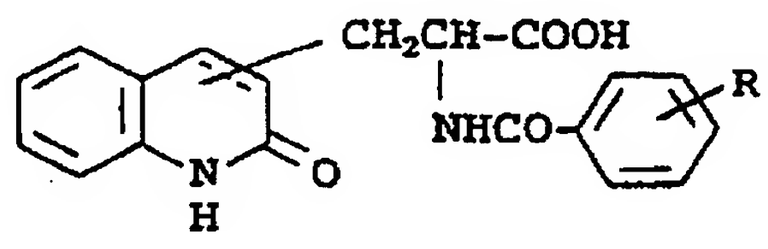
wherein M is an alkali metal, and R, the substituting position of the propionic acid substituent and the bond between 3- and 4-positions are as defined above, with bismuth nitrate.

9. A process for preparing a bismuth salt of a carbostyril derivative of the formula:



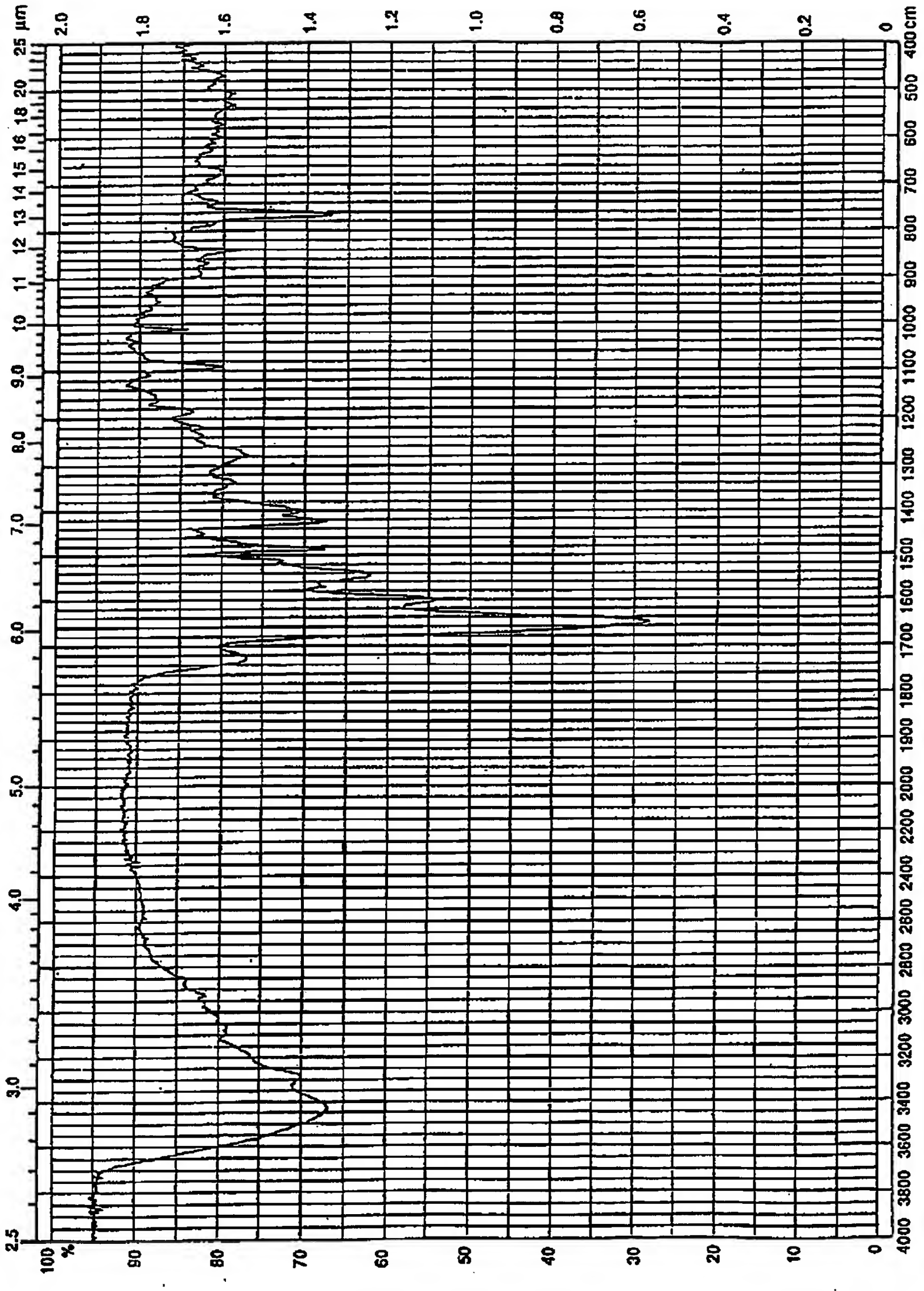
(I)

wherein R is a halogen atom, the propionic acid substituent is substituted at 3- or 4-position on the carbostyril nucleus, and the bond between 3- and 4-positions is single or double bond, which comprises reacting a carbostyril derivative of the formula:



(2b)

wherein R, the substituting position of the propionic acid substituent and the bond between 3- and 4-positions are as defined above, with bismuth hydroxide.


μm
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20
18
16
15
14
13
12
11
10
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.5
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0
cm
400
500
600
700
800
900
1000
1100
1200
1300
1400
1500
1600
1700
1800
1900
2000
2200
2400
2600
2800
3000
3200
3400
3600
3800
4000
%
100
90
80
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60
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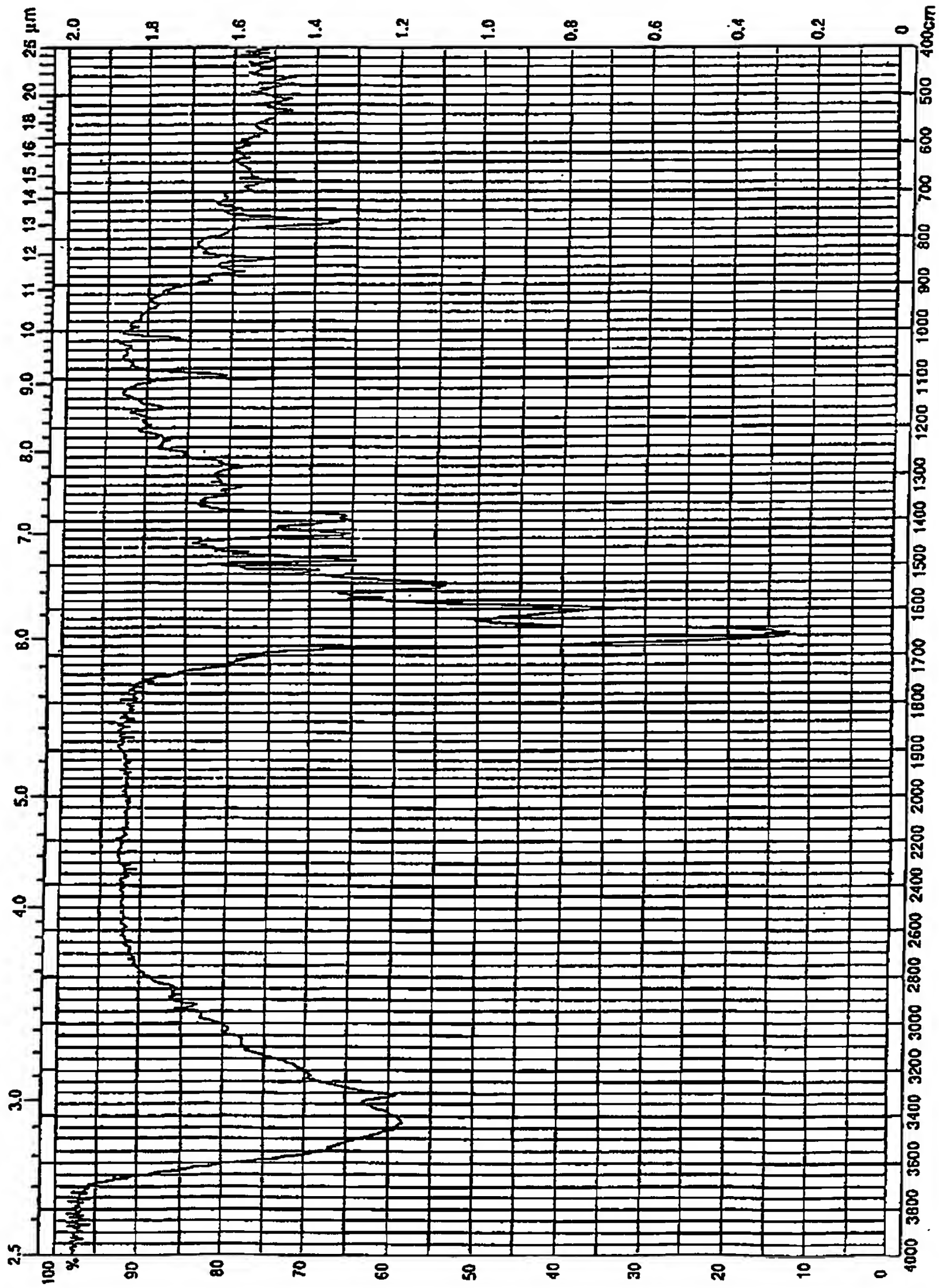
40
30
20
10
0

Fig. 1


μm
25
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9.0
8.0
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6.0
5.0
4.0
3.0
2.5
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0
400cm
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600
700
800
900
1000
1100
1200
1300
1400
1500
1600
1700
1800
1900
2000
2200
2400
2600
2800
3000
3200
3400
3600
3800
4000
%
100
90
80
70
60
50
40
30
20
10
0

Fig. 2

INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/JP 94/01805

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D215/22 A61K31/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE,A,33 24 034 (OTSUKA PHARMACEUTICAL CO., LTD.) 5 January 1984 * page 22, line 1-5; page 136, etc. *	1,6
A	EP,A,0 206 626 (MARSHALL, BARRY JAMES) 30 December 1986 cited in the application see claims	
A	WO,A,92 21342 (OTSUKA PHARMACEUTICAL CO., LTD.) 10 December 1992 cited in the application * abstract *	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 November 1994	-8. 12. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Van Bijlen, H

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/JP 94/01805

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